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Applicants: Jordan J.N. Tang and Arun K. Ghosh

Serial No.: 09/603,713

Art Unit: 1614

Filed: June 27, 2000

Examiner: Not Yet Assigned

For: *INHIBITORS OF MEMAPSIN 2 AND USE THEREOF*

Assistant Commissioner for Patents
Washington, D.C. 20231

INFORMATION DISCLOSURE STATEMENT

Sir:

Pursuant to 37 C.F.R. §1.56 and 37 C.F.R. §1.97, Applicants submit an Information Disclosure Statement, including ten (10) pages of Form PTO-1449 and a copy of each document cited therein.

This Information Disclosure Statement is being filed under 37 C.F.R. § 1.97(b) prior to a first Office Action on the merits. It is believed that no fee is required with this submission. However, should a fee be required, the Commissioner is hereby authorized to charge any required fees to Deposit Account No. 01-2507.

U.S. Patents

<u>Number</u>	<u>Issue Date</u>	<u>Patentee</u>	<u>Class/Subclass</u>
5,200,339	04-06-1993	Abraham	435/212
5,733,768	03-31-1998	Dixon et al.	435/226
5,942,400	08-24-1999	Anderson et al.	435/7.1
5,978,740	11-02-1999	Armistead	702/19
5,986,054	11-16-1999	St. George-Hyslop et al	530/350
6,077,682	06-20-2000	Inouye et al.	435/15

Foreign Documents



<u>Number</u>	<u>Publication Date</u>	<u>Patentee</u>	<u>Country</u>
855 444 A2	07-29-1998	SmithKline Beecham Pharmaceuticals	EP
10 108 681 A	04-28-1998	SmithKline Beecham Corp	JP
WO 96/40885 A2	12-19-1996	Athena Neurosciences, Inc.	PCT
WO 97/27296 A1	07-31-1997	HSC Research and Development Limited	PCT
		Partnership; The Governing Council of the University of Toronto	PCT
WO 98/13488 A2	04-02-1998	Schering Aktiengesellschaft	PCT
WO 98/15828 A1	04-16-1998	Scios, Inc.	PCT
WO 98/21589 A1	05-22-1998	The Trustees of the University of Pennsylvania	PCT
WO 98/26059 A1	05-18-1998	Athena Neurosciences, Inc.	PCT
WO 99/51752 A1	10-14-1999	Chugai Seiyaku Kabushiki Kaisha	PCT

Publications

ABAD-ZAPATERO, et al., "Structure of a secreted aspartic protease from *C. albicans* complexed with a potent inhibitor: implications for the design of antifungal agents," *Protein Sci* 5(4):640-52 (1996).

ABBENATE, et al., "Inhibitors of β -amyloid formation based on the β -secretase cleavage site," *Biochemical and Biophysical Research Communications* 268(1):133-135 (2000).

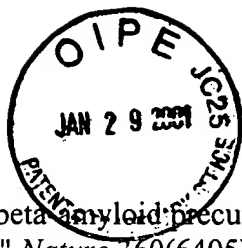
ASKEW, et al., "Molecular recognition with convergent functional groups. Synthetic and structural studies with a model receptor for nucleic acid components," *J. Am. Chem. Soc.* 111, 1082-1090 (1989).

BAILEY & COOPER, "A structural comparison of 21 inhibitor complexes of the aspartic proteinase from *Endothia parasitica*," *Protein Sci* 3(11):2129-43 (1994).

BRUNGER, et al., "Crystallography & NMR system: A new software suite for macromolecular structure determination," *Acta Crystallogr D Biol Crystallogr* 54 (Pt 5):905-21 (1998).

CAPELL, et al., "The proteolytic fragments of the Alzheimer's disease-associated presenilin-1 form heterodimers and occur as a 100-150-kDa molecular mass complex," *J Biol Chem* 273(6):3205-11 (1998).

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CORDER, et al., "Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families," *Science* 261(5123):921-3 (1993).

COWLEY, et al., "Alzheimer's unlocking the mystery," *Newsweek* January 31, 2000.

CUTFIELD, et al., "The crystal structure of a major secreted aspartic proteinase from *Candida albicans* in complexes with two inhibitors," *Structure* 3(11):1261-71 (1995).

DAVIES, "The structure and function of the aspartic proteinases," *Annu Rev Biophys Chem* 19:189-215 (1990).

DEALWIS, et al., "X-ray analysis at 2.0 Å resolution of mouse submaxillary renin complexed with a decapeptide inhibitor CH-66, based on the 4-16 fragment of rat angiotensinogen," *J. Mol. Biol.* 236(1):342-60 (1994).

DE STROOPER, et al., "Deficiency of presenilin-1 inhibits the normal cleavage of amyloid precursor protein," *Nature* 391(6665):387-90 (1998).

DUNN, Structure and Functions of the Aspartic Proteinases, Adv. in Exptl. Med. Biol. 306 (Plenum Press, NY 1991).

ELLINGTON & SZOSTAK, "In vitro selection of RNA molecules that bind specific ligands," *Nature* 346(6287):818-22 (1990).

FAN, et al., "*BACE* Maps to chromosome 11 and a *BACE* homolog, *BACE2*, reside in the obligate down syndrome region of chromosome 21," *Science* 286:1255a (1999).

FIELDS & SONG, "A novel genetic system to detect protein-protein interactions," *Nature* 340(6230):245-6 (1989).

GHOSH & FIDANZE, Transition-state mimetics for HIV protease inhibitors: Stereocontrolled synthesis of hydroxyethylene and hydroxyethylamine isosteres by ester-derived titanium enolate syn and anti-aldol reactions," *Org. Chem.* 63:6146-54 (1998).

GLENNER & WONG, "Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein," *Biochem Biophys Res Commun* 120(3):885-90 (1984).

GOATE, et al., "Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease," *Nature* 349(6311):704-6 (1991).

GOLDGABER, et al., "Characterization and chromosomal localization of a cDNA encoding brain amyloid of Alzheimer's disease," *Science* 235(4791):877-80 (1987).

HAASS & DE STROOPER, "The presenilins in Alzheimer's disease--Proteolysis holds the key," *Science* 286:916-919 (1999).

JAMES, Aspartic Proteinases, Retroviral and Cellular Enzymes, Adv. in Exptl. Med. Biol. 436 (Plenum Press, NY 1998).

JONES, et al., "Improved methods for binding protein models in electron density maps and the location of errors in these models" *Acta Crystallogr A* 47 (Pt 2):110-9 (1991).

JORM, ed., A Guide to the Understanding of Alzheimer's Disease and Related Disorders (New York University Press, New York 1987).

KANG, et al., "The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor," *Nature* 325(6106):733-6 (1987).

KEARNEY & AWEEKKA, "The penetration of anti-infectives into the central nervous system," *Neurol. Clin.* 17(4):883-900 (1999).

KELLY & DOW, "Microbial differentiation: the role of cellular asymmetry," *Microbiol Sci* 1(9):214-9 (1984).

KHAN, et al., "Lowering the entropic barrier for binding conformationally flexible inhibitors to enzymes," *Biochemistry* 37(48):16839-45 (1998).

KNOPS, et al., "Cell-type and amyloid precursor protein-type specific inhibition of A beta release by bafilomycin A1, a selective inhibitor of vacuolar ATPases," *J Biol Chem* 270(6):2419-22 (1995).

KOLATA, "Scientists find enzyme linked to Alzheimer's," National Science/Health October 22, 1999.

KOSTKA, Aspartic proteinases and Their Inhibitor (Walter de Gruyter, Berlin 1985).

LASKOWSKI, et al., "Procheck: a program to check the stereochemical quality of protein structures," *J Appl. Crystallog* 26:283 (1993).

LEMAIRE, et al., "The PreA4(695) precursor protein of Alzheimer's disease A4 amyloid is encoded by 16 exons," *Nucleic Acids Res* 17(2):517-22 (1989).

LEVY, et al., "Mutation of the Alzheimer's disease amyloid gene in hereditary cerebral hemorrhage, Dutch type," *Science* 248(4959):1124-6 (1990).

LEVY-LAHAD, et al., "Candidate gene for the chromosome 1 familial Alzheimer's disease locus," *Science* 269(5226):973-7 (1995).

LEWIS & DEAN, "Automated site-directed drug design: the concept of spacer skeletons for primary structure generation," *Proc R Soc Lond B Biol Sci* 236(1283):125-40 and 141-162 (1989).

LIN, et al., "Intracellular diversion of glycoprotein GP160 of human immunodeficiency virus to lysosomes as a strategy of AIDS gene therapy," *FASEB J* 7(11):1070-80 (1993).

MANN, "Cerebral amyloidosis, ageing and Alzheimer's disease; a contribution from studies on Down's syndrome," *Neurobiol Aging* 10(5):397-9 (1989).

MARCINISZYN, et al., "Mode of inhibition of acid proteases by pepstatin," *J. Biol. Chem.* 251(22):7088-94 (1976).

MATSUMOTO, et al., "Molecular cloning of human cDNA with a sequence highly similar to that of the dihydrofolate reductase gene in brain libraries derived from Alzheimer's disease patients," *Eur. J. Biochem.* 230:337-343 (1995).

MECKELEIN, et al., "Identification of a novel serine protease-like molecule in human brain," *Molecular Brain Research* 55:181-197 (1998).

MCKINLAY & ROSSMANN, "Rational design of antiviral agents," *Annu Rev Pharmacol Toxicol* 29:111-22 (1989).

MULLAN, et al., "A locus for familial early-onset Alzheimer's disease on the long arm of chromosome 14, proximal to the alpha 1-antichymotrypsin gene," *Nat Genet* 2(4):340-2 (1992).

MULLAN, et al., "A pathogenic mutation for probable Alzheimer's disease in the APP gene at the N-terminus of beta-amyloid," *Nat Genet* 1(5):345-7 (1992).

MURRELL, et al., "A mutation in the amyloid precursor protein associated with hereditary Alzheimer's disease," *Science* 254(5028):97-9 (1991).

NAVAZA, "AMoRe: an automated package for molecular replacement," *Acta Crystallog Sect A* 50:157 (1997).

OTWINOWSKI & MINOR, "Processing of X-ray diffraction data collected in Oscillation mode," *Methods Enzymol* 276:307 (1997).

PEREZ, et al., "Enhanced release of amyloid beta-protein from codon 670/671 "Swedish" mutant beta-amyloid precursor protein occurs in both secretory and endocytic pathways," *J Biol Chem* 271(15):9100-7 (1996).

PERRY & DAVIES, QSAR: Quantitative Structure-Activity Relationships in Drug Design pp. 189-193 (Alan R. Liss, Inc. 1989).

PHIMISTER, "Four companies announce discovery of b-secretase gene," *Nature Biotechnology* 18:16 (2000).

PODLISNY, et al., "Presenilin proteins undergo heterogeneous endoproteolysis between Thr291 and Ala299 and occur as stable N- and C-terminal fragments in normal and Alzheimer brain tissue," *Neurobiol Dis* 3(4):325-37 (1997).

RIPKA, "Computers picture the perfect drug," *New Scientist* 54-57 (1988).

ROBAKIS, et al., "Molecular cloning and characterization of a cDNA encoding the cerebrovascular and the neuritic plaque amyloid peptides," *Proc Natl Acad Sci U S A* 84(12):4190-4 (1987).

ROBERTS & SZOSTAK, "RNA-peptide fusions for the in vitro selection of peptides and proteins," *Proc Natl Acad Sci U S A* 94(23):12297-302 (1997).

ROGAEV, et al., "Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene," *Nature* 376(6543):775-8 (1995).

ROUVINEN, et al., "Computer aided drug design," *Acta Pharmaceutica Fennica* 97, 159-166 (1988).

RUMBLE, et al., "Amyloid A4 protein and its precursor in Down's syndrome and Alzheimer's disease," *N Engl J Med* 320(22):1446-52 (1989).

SELKOE, et al., "Translating cell biology into therapeutic advances in Alzheimer's disease," *Nature* 399(6738 Suppl):A23-31 (1999).

SHERINGTON, et al., "Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease," *Nature* 375(6534):754-60 (1995).

SINHA & LIEBERBURG, "Cellular mechanisms of beta-amyloid production and secretion," *Proc Natl Acad Sci U S A* 96(20):11049-53 (1999).

SINHA, et al., "Purification and cloning of amyloid precursor protein beta-secretase from human brain," *Nature* 402(6761):537-40 (1999).

STEINER, et al., "Expression of Alzheimer's disease-associated presenilin-1 is controlled by proteolytic degradation and complex formation," *J Biol Chem* 273(48):32322-31 (1998).

SUZUKI, et al., "An increased percentage of long amyloid beta protein secreted by familial amyloid beta protein precursor (beta APP717) mutants," *Science* 264(5163):1336-40 (1994).

SYMERSKY, et al., "High-resolution structure of the extracellular aspartic proteinase from *Candida tropicalis* yeast," *Biochemistry* 36(42):12700-10 (1997).

SZOSTAK, "In vitro genetics," *TIBS* 19:89, (1992).

TAGAWA, et al., "Alzheimer's disease amyloid β -clipping enzyme (APP secretase): Identification, purification, and characterization of the enzyme," *Biochemical and Biophysical Research Communications* 177(1):377-387 (1991).

TAKAHASHI, Aspartic Proteases, Structure, Function, Biology, Biomedical Implications, Adv. in Exptl. Med. Biol. 362 (Plenum Press, NY 1995).

TANG, Acid Proteases, Structure, Function and Biology, Adv. in Exptl. Med. Biol. vol. 95 (Plenum Press, NY 1977).

TANG, et al., "Structural evidence for gene duplication in the evolution of the acid proteases," *Nature* 271(5646):618-21 (1978).

TANZI, et al., "Protease inhibitor domain encoded by an amyloid protein precursor mRNA associated with Alzheimer's disease," *Nature* 331(6156):528-30 (1988).

The early story of Alzheimer's Disease, edited by Bick et al. (Raven Press, New York 1987).

THINAKARAN, et al., "Endoproteolysis of presenilin 1 and accumulation of processed derivatives in vivo," *Neuron* 17(1):181-90 (1996).

THINAKARAN, et al., "Evidence that levels of presenilins (PS1 and PS2) are coordinately regulated by competition for limiting cellular factors," *J Biol Chem* 272(45):28415-22 (1997).

THINAKARAN, et al., "Stable association of presenilin derivatives and absence of presenilin interactions with APP," *Neurobiol Dis* 4(6):438-53 (1998).

VAN BROECKHOVEN, et al., "Amyloid beta protein precursor gene and hereditary cerebral hemorrhage with amyloidosis (Dutch)," *Science* 248(4959):1120-2 (1990).

VASSAR, et al., "Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE," *Science* 286(5440):735-41 (1999).

WOLFE, et al., "Two transmembrane aspartates in presenilin-1 required for presenilin endoproteolysis and gamma-secretase activity," *Nature* 398(6727):513-7 (1999).

YANG & QUAIL, "Structure of the *Rhizomucor miehei* aspartic proteinase complexed with the inhibitor pepstatin A at 2.7 Å resolution," *Acta Crystallogr D Biol Crystallogr* 55 (Pt 3):625-30 (1999).

YOSHIKAI, et al., "Genomic organization of the human amyloid beta-protein precursor gene," *Gene* 87(2):257-63 (1990).

YU, "Inhibition of beta-amyloid cytotoxicity by midkine," *Neurosci Lett* 254(3):125-8 (1998).

Remarks

This statement should not be interpreted as a representation that an exhaustive search has been conducted or that no better art exists. Moreover, Applicants invite the Examiner to make an independent evaluation of the cited art to determine its relevance to the subject matter of the present application. Applicants are of the opinion that their claims patentably distinguish over the art referred to herein, either alone or in combination.

Respectfully submitted,

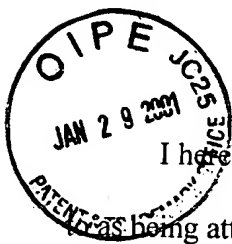


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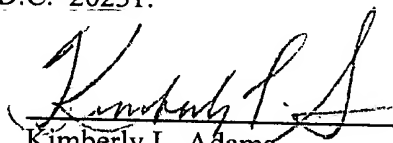
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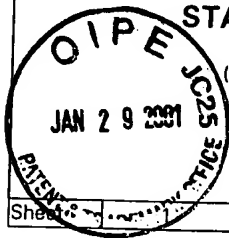

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STATEMENT BY APPLICANT**

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Application Number	09/603,713
Filing Date	June 27, 2000
First Named Inventor	Jordan J. N. Tang
Group Art Unit	1614
Examiner Name	
Attorney Docket Number	OMRF 182

Sheet 1 of 10

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No. ¹	US Patent Document Number Kind Code ² (if known)	Name of Patentee or Applicant of Cited Document	Date of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		5,200,339	Abraham	04-06-1993	
		5,733,768	Dixon et al.	03-31-1998	
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		6,077,682	Inouye et al.	06-20-2000	

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		Office ³	Number ⁴	Kind Code ⁵ (if known)				
		EP	0 855 444	A2	SmithKline Beecham Pharmaceuticals	07-29-1998		
		JP	10 108 681	A	SmithKline Beecham Corp	04-28-1998		
		WO	96/40885	A2	Athena Neurosciences, Inc.	12-19-1996		
		WO	97/27296	A1	HSC Research and Development Limited Partnership; The Governing Council of the University of Toronto	07-31-1997		
		WO	98/13488	A2	Schering Aktiengesellschaft	04-02-1998		
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		WO	98/21589	A1	The Trustees of the University of Pennsylvania	05-22-1998		
		WO	98/26059	A1	Athena Neurosciences, Inc.	05-18-1998		
		WO	99/51752	A1	Chugai Seiyaku Kabushiki Kaisha	10-14-1999		

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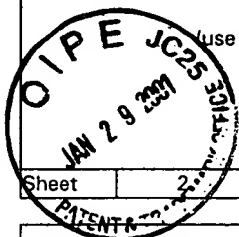
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		ABAD-ZAPATERO, et al., "Structure of a secreted aspartic protease from <i>C. albicans</i> complexed with a potent inhibitor: implications for the design of antifungal agents," <i>Protein Sci</i> 5(4):640-52 (1996).	
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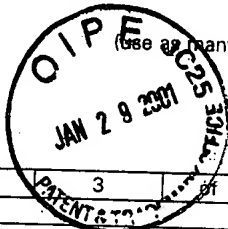
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OTHER ART -- NON-PATENT LITERATURE DOCUMENTS

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		COWLEY, et al., "Alzheimer's unlocking the mystery," <i>Newsweek</i> January 31, 2000.	
		CUTFIELD, et al., "The crystal structure of a major secreted aspartic proteinase from <i>Candida albicans</i> in complexes with two inhibitors," <i>Structure</i> 3(11):1261-71 (1995).	
		DAVIES, "The structure and function of the aspartic proteinases," <i>Annu Rev Biophys Chem</i> 19:189-215 (1990).	
		DE STROOPER, et al., "Deficiency of presenilin-1 inhibits the normal cleavage of amyloid precursor protein," <i>Nature</i> 391(6665):387-90 (1998).	
		DEALWIS, et al., "X-ray analysis at 2.0 Å resolution of mouse submaxillary renin complexed with a decapeptide inhibitor CH-66, based on the 4-16 fragment of rat angiotensinogen," <i>J. Mol. Biol.</i> 236(1):342-60 (1994).	
		DUNN, Structure and Functions of the Aspartic Proteinases, <i>Adv. in Exptl. Med. Biol.</i> 306 (Plenum Press, NY 1991).	
		ELLINGTON & SZOSTAK, "In vitro selection of RNA molecules that bind specific ligands," <i>Nature</i> 346(6287):818-22 (1990).	
		FAN, et al., "BACE Maps to chromosome 11 and a BACE homolog, BACE2, reside in the obligate down syndrome region of chromosome 21," <i>Science</i> 286:1255a (1999).	
		FIELDS & SONG, "A novel genetic system to detect protein-protein interactions," <i>Nature</i> 340(6230):245-6 (1989).	
		GHOSH & FIDANZE, Transition-state mimetics for HIV protease inhibitors: Stereocontrolled synthesis of hydroxyethylene and hydroxyethylamine isosteres by ester-derived titanium enolate syn and anti-aldol reactions," <i>Org. Chem.</i> 63:6146-54 (1998).	

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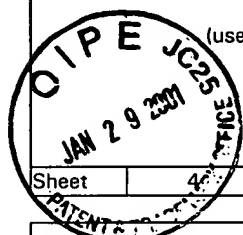
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STATEMENT BY APPLICANT**

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Application Number	09/603,713
Filing Date	June 27, 2000
First Named Inventor	Jordan J. N. Tang
Group Art Unit	1614
Examiner Name	
Attorney Docket Number	OMRF 182



Sheet 4 of 10

OTHER ART -- NON-PATENT LITERATURE DOCUMENTS

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		GLENNER & WONG, "Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein," <i>Biochem Biophys Res Commun</i> 120(3):885-90 (1984).	
		GOATE, et al., "Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease," <i>Nature</i> 349(6311):704-6 (1991).	
		GOLDGABER, et al., "Characterization and chromosomal localization of a cDNA encoding brain amyloid of Alzheimer's disease," <i>Science</i> 235(4791):877-80 (1987).	
		HAASS & DE STROOPER, "The presenilins in Alzheimer's disease--Proteolysis holds the key," <i>Science</i> 286:916-919 (1999).	
		JAMES, Aspartic Proteinases, Retroviral and Cellular Enzymes, Adv. in Exptl. Med. Biol. 436 (Plenum Press, NY 1998).	
		JONES, et al., "Improved methods for binding protein models in electron density maps and the location of errors in these models" <i>Acta Crystallogr A</i> 47 (Pt 2):110-9 (1991).	
		JORM, ed., <i>A Guide to the Understanding of Alzheimer's Disease and Related Disorders</i> (New York University Press, New York 1987).	
		KANG, et al., "The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor," <i>Nature</i> 325(6106):733-6 (1987).	
		KEARNEY & AWEEKA, "The penetration of anti-infectives into the central nervous system," <i>Neurol. Clin.</i> 17(4):883-900 (1999).	
		KELLY & DOW, "Microbial differentiation: the role of cellular asymmetry," <i>Microbiol Sci</i> 1(9):214-9 (1984).	

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		Filing Date	June 27, 2000
		First Named Inventor	Jordan J. N. Tang
		Group Art Unit	1614
		Examiner Name	
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		KHAN, et al., "Lowering the entropic barrier for binding conformationally flexible inhibitors to enzymes," <i>Biochemistry</i> 37(48):16839-45 (1998).
		KNOPS, et al., "Cell-type and amyloid precursor protein-type specific inhibition of A beta release by bafilomycin A1, a selective inhibitor of vacuolar ATPases," <i>J Biol Chem</i> 270(6):2419-22 (1995).
		KOLATA, "Scientists find enzyme linked to Alzheimer's," <i>National Science/Health</i> October 22, 1999.
		KOSTKA, <u>Aspartic proteinases and Their Inhibitor</u> (Walter de Gruyter, Berlin 1985).
		LASKOWSKI, et al., "Procheck: a program to check the stereochemical quality of protein structures," <i>J Appl. Crystallog</i> 26:283 (1993).
		LEMAIRE, et al., "The PreA4(695) precursor protein of Alzheimer's disease A4 amyloid is encoded by 16 exons," <i>Nucleic Acids Res</i> 17(2):517-22 (1989).
		LEVY, et al., "Mutation of the Alzheimer's disease amyloid gene in hereditary cerebral hemorrhage, Dutch type," <i>Science</i> 248(4959):1124-6 (1990).
		LEVY-LAHAD, et al., "Candidate gene for the chromosome 1 familial Alzheimer's disease locus," <i>Science</i> 269(5226):973-7 (1995).
		LEWIS & DEAN, "Automated site-directed drug design: the concept of spacer skeletons for primary structure generation," <i>Proc R Soc Lond B Biol Sci</i> 236(1283):125-40 and 141-162 (1989).
		LIN, et al., "Intracellular diversion of glycoprotein GP160 of human immunodeficiency virus to lysosomes as a strategy of AIDS gene therapy," <i>FASEB J</i> 7(11):1070-80 (1993).

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				Application Number	09/603,713
				Filing Date	June 27, 2000
				First Named Inventor	Jordan J. N. Tang
				Group Art Unit	1614
				Examiner Name	
Sheet	6	of	10	Attorney Docket Number	OMRF 182

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		MANN, "Cerebral amyloidosis, ageing and Alzheimer's disease; a contribution from studies on Down's syndrome," <i>Neurobiol Aging</i> 10(5):397-9 (1989).	
		MARCINISZYN, et al., "Mode of inhibition of acid proteases by pepstatin," <i>J. Biol. Chem.</i> 251(22):7088-94 (1976).	
		MATSUMOTO, et al., "Molecular cloning of human cDNA with a sequence highly similar to that of the dihydrofolate reductase gene in brain libraries derived from Alzheimer's disease patients," <i>Eur. J. Biochem.</i> 230:337-343 (1995).	
		MCKINLAY & ROSSMANN, "Rational design of antiviral agents," <i>Annu Rev Pharmacol Toxicol</i> 29:111-22 (1989).	
		MECKELEIN, et al., "Identification of a novel serine protease-like molecule in human brain," <i>Molecular Brain Research</i> 55:181-197 (1998).	
		MULLAN, et al., "A locus for familial early-onset Alzheimer's disease on the long arm of chromosome 14, proximal to the alpha 1-antichymotrypsin gene," <i>Nat Genet</i> 2(4):340-2 (1992).	
		MULLAN, et al., "A pathogenic mutation for probable Alzheimer's disease in the APP gene at the N-terminus of beta-amyloid," <i>Nat Genet</i> 1(5):345-7 (1992).	
		MURRELL, et al., "A mutation in the amyloid precursor protein associated with hereditary Alzheimer's disease," <i>Science</i> 254(5028):97-9 (1991).	
		NAVAZA, "AMoRe: an automated package for molecular replacement," <i>Acta Crystallog Sect A</i> 50:157 (1997).	
		OTWINOWSKI & MINOR, "Processing of X-ray diffraction data collected in Oscillation mode," <i>Methods Enzymol</i> 276:307 (1997).	

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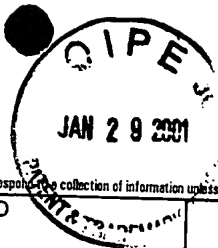
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Application Number	09/603,713
Filing Date	June 27, 2000
First Named Inventor	Jordan J. N. Tang
Group Art Unit	1614
Examiner Name	
Attorney Docket Number	OMRF 182

Sheet 7 of 10

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		PEREZ, et al., "Enhanced release of amyloid beta-protein from codon 670/671 "Swedish" mutant beta-amyloid precursor protein occurs in both secretory and endocytic pathways," J Biol Chem 271(15):9100-7 (1996).	
		PERRY & DAVIES, <u>QSAR: Quantitative Structure-Activity Relationships in Drug Design</u> pp. 189-193 (Alan R. Liss, Inc. 1989).	
		PHIMISTER, "Four companies announce discovery of b-secretase gene," <i>Nature Biotechnology</i> 18:16 (2000).	
		PODLISNY, et al., "Presenilin proteins undergo heterogeneous endoproteolysis between Thr291 and Ala299 and occur as stable N- and C-terminal fragments in normal and Alzheimer brain tissue," <i>Neurobiol Dis</i> 3(4):325-37 (1997).	
		RIPKA, "Computers picture the perfect drug," <i>New Scientist</i> 54-57 (1988).	
		ROBAKIS, et al., "Molecular cloning and characterization of a cDNA encoding the cerebrovascular and the neuritic plaque amyloid peptides," <i>Proc Natl Acad Sci U S A</i> 84(12):4190-4 (1987).	
		ROBERTS & SZOSTAK, "RNA-peptide fusions for the in vitro selection of peptides and proteins," <i>Proc Natl Acad Sci U S A</i> 94(23):12297-302 (1997).	
		ROGAEV, et al., "Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene," <i>Nature</i> 376(6543):775-8 (1995).	
		ROUVINEN, et al., "Computer aided drug design," <i>Acta Pharmaceutica Fennica</i> 97, 159-166 (1988).	
		RUMBLE, et al., "Amyloid A4 protein and its precursor in Down's syndrome and Alzheimer's disease," <i>N Engl J Med</i> 320(22):1446-52 (1989).	

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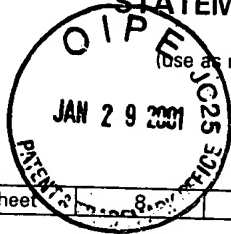
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary) 		Application Number		09/603,713
		Filing Date		June 27, 2000
		First Named Inventor		Jordan J. N. Tang
		Group Art Unit		1614
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Attorney Docket Number		OMRF 182		

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		SELKOE, et al., "Translating cell biology into therapeutic advances in Alzheimer's disease," Nature 399(6738 Suppl):A23-31 (1999).	
		SHERRINGTON, et al., "Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease," Nature 375(6534):754-60 (1995).	
		SINHA & LIEBERBURG, "Cellular mechanisms of beta-amyloid production and secretion," Proc Natl Acad Sci U S A 96(20):11049-53 (1999).	
		SINHA, et al., "Purification and cloning of amyloid precursor protein beta-secretase from human brain," Nature 402(6761):537-40 (1999).	
		STEINER, et al., "Expression of Alzheimer's disease-associated presenilin-1 is controlled by proteolytic degradation and complex formation," J Biol Chem 273(48):32322-31 (1998).	
		SUZUKI, et al., "An increased percentage of long amyloid beta protein secreted by familial amyloid beta protein precursor (beta APP717) mutants," Science 264(5163):1336-40 (1994).	
		SYMERSKY, et al., "High-resolution structure of the extracellular aspartic proteinase from Candida tropicalis yeast," Biochemistry 36(42):12700-10 (1997).	
		SZOSTAK, "In vitro genetics," TIBS 19:89, (1992).	
		TAGAWA, et al., "Alzheimer's disease amyloid -clipping enzyme (APP secretase): Identification, purification, and characterization of the enzyme," Biochemical and Biophysical Research Communications 177(1):377-387 (1991).	
		TAKAHASHI, Aspartic Proteases, Structure, Function, Biology, Biomedical Implications, Adv. in Exptl. Med. Biol. 362 (Plenum Press, NY 1995).	

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		Filing Date	June 27, 2000
		First Named Inventor	Jordan J. N. Tang
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Sheet 9	10	Attorney Docket Number	OMRF 182

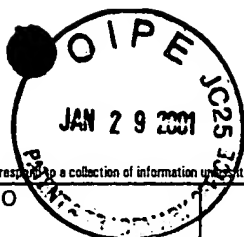
OTHER ART -- NON PATENT LITERATURE DOCUMENTS			
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		TANG, Acid Proteases, Structure, Function and Biology, Adv. in Exptl. Med. Biol. vol. 95 (Plenum Press, NY 1977).	
		TANG, et al., "Structural evidence for gene duplication in the evolution of the acid proteases," Nature 271(5646):618-21 (1978).	
		TANZI, et al., "Protease inhibitor domain encoded by an amyloid protein precursor mRNA associated with Alzheimer's disease," Nature 331(6156):528-30 (1988).	
		<i>The early story of Alzheimer's Disease</i> , edited by Bick et al. (Raven Press, New York 1987).	
		THINAKARAN, et al., "Endoproteolysis of presenilin 1 and accumulation of processed derivatives in vivo," Neuron 17(1):181-90 (1996).	
		THINAKARAN, et al., "Evidence that levels of presenilins (PS1 and PS2) are coordinately regulated by competition for limiting cellular factors," J Biol Chem 272(45):28415-22 (1997).	
		THINAKARAN, et al., "Stable association of presenilin derivatives and absence of presenilin interactions with APP," Neurobiol Dis 4(6):438-53 (1998).	
		VAN BROECKHOVEN, et al., "Amyloid beta protein precursor gene and hereditary cerebral hemorrhage with amyloidosis (Dutch)," Science 248(4959):1120-2 (1990).	
		VASSAR, et al., "Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE," Science 286(5440):735-41 (1999).	
		WOLFE, et al., "Two transmembrane aspartates in presenilin-1 required for presenilin endoproteolysis and gamma-secretase activity," Nature 398(6727):513-7 (1999).	

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		YANG & QUAIL, "Structure of the Rhizomucor miehei aspartic proteinase complexed with the inhibitor pepstatin A at 2.7 Å resolution," Acta Crystallogr D Biol Crystallogr 55 (Pt 3):625-30 (1999).	
		YOSHIKAI, et al., "Genomic organization of the human amyloid beta-protein precursor gene," Gene 87(2):257-63 (1990).	
		YU, "Inhibition of beta-amyloid cytotoxicity by midkine," Neurosci Lett 254(3):125-8 (1998).	

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